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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,080	10/08/2004	J. Phillip Bowen	B40-002	3420

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COLEMAN SUDOL SAPONE, P.C.
714 COLORADO AVENUE
BRIDGE PORT, CT 06605-1601

EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
07/06/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/502,080	BOWEN ET AL.
	Examiner	Art Unit
	PAUL ZAREK	1628

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,50-56 and 67-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,50-56 and 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/28/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that Examiner Paul Zarek is now examining the instant application. Applicants are respectfully requested to direct all communication to Examiner Zarek. Please see contact information below.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 02/28/2011 and 04/28/2011 have been entered.

Status of the Claims

3. Claims 50 and 53 have been amended, Claim 67 has been added, and Claims 66 has been cancelled by the Applicant in correspondence filed on 02/28/2011. Claims 68 and 69 have been added by Applicant in correspondence filed on 04/28/2011. Claims 40, 50-56, and 67-69 are currently pending. This is the first Office Action on the merits of the claim(s) following a request for continued examination.

Information Disclosure Statement

4. The IDS filed on 09/28/2010 is acknowledged and the information contained therein has been considered.

RESPONSE TO ARGUMENTS

5. Claim 50 was objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. This objection is moot in light of Applicants' amendment to Claim 50.

6. Claims 40, 51-56 and 66 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claim 66 has been cancelled. Applicants traversed this rejection on the grounds that the instant specification fully enables the instantly claimed invention. Specifically, Applicants contend that the instant specification demonstrates that solenopsin inhibits angiogenesis, both directly and indirectly. Applicants provide Arbiser, et al. (Blood, 2007), and Park, et al. (Journal of Infectious Diseases, 2008), as evidence that solenopsin is a phosphatidylinositol-3-kinase (PI3K) inhibitor and is "an ideal compound for providing generic therapy against a variety of cancerous tissue" and that its use as an anticancer agent is "consistent with its activity as an inhibitor of angiogenesis" since PI3K inhibitors are known to display anti-angiogenic properties. Applicants also provide the Arbiser Declaration (filed 02/28/2011) which states that angiogenesis is integral to the formation of solid tumors (among other conditions) and inhibiting angiogenesis is currently being used clinically with Avastin (bevacizumab). The Arbiser Declaration provides *in vitro* evidence that solenopsin inhibits proliferation of two tumor cell lines. Given the *in vitro* antiproliferative effect of solenopsin and its capacity as a PI3K inhibitor, Dr. Arbiser concludes that solenopsin would be generically

effective against treating all of the tumors and cancers of the rejected claims. Respectfully, Examiner does not find Applicants' argument persuasive.

7. At the time of the invention, solenopsin was not known for use in treating any form of cancer. The compound was known prior to this application and has been used to treat parasitic infections (Rehmert, US Patent no. 4,910,209, already of record) and to suppress fire ants (Bowen, et al., US Patent no. 6,369,078, already of record). The instant specification discloses that solenopsin can inhibit proliferation of SVR cells at two concentrations of the drug, *in vitro*. SVR cells are murine endothelial tumor cells that have been transformed with SV40 large T antigen and H-ras. Based on these result, the instant specification suggests that all of the instantly claimed tumors and cancers are amenable to therapy by solenopsin. However, it is unclear how Applicants can draw such a conclusion based on the information in the specification and the art at the time of filing.

8. Examiner notes that either 1 μg/mL or 6 μg/mL solenopsin enhances, rather than inhibits, proliferation of SVR cells (Figure 5). This was first noted in Office Action mailed on 06/30/2010. Neither the instant specification nor Applicants' responses have explained this inconsistency demonstrated in Figure 5. Furthermore, even if the data of Figure 5 unequivocally showed that solenopsin inhibits SVR cell proliferation, the art explicitly states that many anticancer agents that appear effective *in vitro* do not translate to a clinically beneficial drug. The agents most likely to be effective chemotherapeutics are those that demonstrate anti-cancer effects in multiple *in vitro* and/or *in vivo* assays. See the discussion of Johnson, et al. (British Journal of Cancer, 2001), Voskoglou-Nomikos, et al. (Clinical Cancer Research, 2003), and Suggitt, et al. (Clinical Cancer Research, 2005) in Office Action mailed 06/03/2010 (pgs 4-7).

Thus, the ordinarily skilled artisan would have no reasonable expectation that solenopsin would effectively treat all or any of the claimed tumors or cancers based solely on the results of the instant specification. Applicants cannot rely on the state of the art at the time of filing to compensate for the deficiencies in the instant specification.

9. Compounds that demonstrate an anti-proliferative effect of SVR cells are not necessarily anti-tumor or anti-cancer agents that are effective against all or most of the instantly claimed tumors or cancers. The instant specification refers to Arbiser, et al. (Journal of the American Academy of Dermatology, 1999), when describing the assay of Figure 5. The authors demonstrate that TNP-470 inhibits proliferation of SVR cells, *in vitro* (Figure 1A) and reduces tumor burden, *in vivo* (Figure 3). Yanase, et al. (Cancer Research, 1993), show that TNP-470 is effective against choriocarcinomas but ineffective against Nakajima ovarian endometrial cancer, *in vitro* (pg 2567, col 2, para 2, ln 4-6; Figure 1C) and *in vivo* (pg 2567, col 2, para 3, final sentence; Table 2). Thus, one cannot directly extrapolate the antiproliferative results of Figure 5 to indicate that solenopsin is effective against all of the claimed tumors and/or cancers.

10. Angiogenesis inhibition is not a "magic bullet" that is effective against all cancers or tumors. Bevacizumab, as noted in the Arbister Declaration, is currently in use for the treatment of kidney and colon cancer. However, it is not effective against all cancers. For example, the FDA recently decided that bevacizumab, an antiangiogenic agent, is not indicated for breast cancer due, in part, to a lack of beneficial effect (para 4, ln 3). See also Calabresi and Chabner (Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed., 2001, already of record).

11. Applicants' arguments regarding the alleged PI3K inhibitory properties of solenopsin are not persuasive. The instant application discusses solenopsin as an anti-angiogenic agent. This property exists regardless of its mechanism of action, PI3K inhibition or other. As such, it is unclear how the mechanism of action of solenopsin supports enablement of the instantly claimed method to treat a number of tumors and cancers that are not necessarily pathologically related to each other. Just as the anti-angiogenic agent bevavizumab is not indicated for all cancers, the art worker would not expect that a PI3K inhibitor would be effective for all cancers. In sum, the art warns against extrapolating too much from a single anti-cancer assay and indicates that there is no "magic bullet" that is to be expected to be effective against all or most cancers. The instant specification and Applicants' arguments are not sufficient to overcome the teachings in the art. Therefore, the rejection of Claims 40 and 50-56 under 35 U.S.C. 112, first paragraph, is maintained.

12. Applicants can overcome this rejection by demonstrating that solenopsin consistently inhibits cancer cell proliferation in various models of tumors and/or cancer.

13. New grounds of rejections and objections over Claims 40, 50-57, and 63-65 are provided below. This rejection is **non-final**.

Drawings

14. The drawings are objected to because it is unclear which bar corresponds to 1 μg/mL and which bar corresponds to 6 μg/mL. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any

amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112 (1st paragraph)

15. The text of Title 35, U.S.C. § 112, first paragraph, can be found in a prior Office action.

16. Claims 67-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific tumors cancers with solenopsin, does not reasonably provide enablement for treating all of the tumors and cancer of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

17. The reasoning for this rejection is discussed above and previously and is applied to Claim 67-69 in the same manner as previously discussed.

Conclusion

18. Claims 40, 50-57, and 67-69 are rejected.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL ZAREK whose telephone number is (571)270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Paul Zarek/
Examiner, Art Unit 1628